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SUBJECT: DRAFT FINDINGS ON THE HEALTH EFFECTS OF THE ACTIVE INGREDIENT: METHIDATHION

Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) draft findings for the active ingredient methidathion. These draft findings were prepared in response to the risk characterization document (RCD, dated June, 2001), the draft addendum to the RCD (dated October 3, 2003) and final exposure assessment (EAD, dated July 22, 2003) for methidathion prepared by the Department of Pesticide Regulation (DPR). The information contained in these documents served to identify methidathion as a candidate toxic air contaminant (TAC).

Pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides review, consultation and comments to DPR on the evaluation of the health effects of candidate toxic air contaminants (TAC) included in the TAC documents. As part of its statutory responsibility, OEHHA also prepares findings on the health effects of the candidate toxic air contaminants. This documentation is to be included as part of the DPR report.

Should you have any questions regarding OEHHA's draft findings on the health effects of methidathion, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or Dr. Anna M. Fan at (510) 622-3165.

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Office of Environmental Health Hazard Assessment's Findings On the Health Effects of Methidathion

Pursuant to Food and Agricultural Code Sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency provides consultation and technical assistance to the Department of Pesticide Regulation (DPR) on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepares health-based findings. OEHHA previously reviewed and commented on the draft documents prepared by DPR on the evaluation of human health risks associated with potential exposure to methidathion. These documents are used by DPR in considering listing methidathion as a toxic air contaminant (TAC). As part of its statutory responsibility, OEHHA has also prepared these findings on the health effects of methidathion which are to be included as part of DPR's Risk Characterization / Toxic Air Contaminant (RCD/TAC) documents.

Environmental Fate and Exposure

1. Methidathion is a non-systemic organophosphate insecticide registered for the control of a wide range of agricultural mite and insect pests in terrestrial food crops**.** The chemical is used to protect plants from insects with sucking, chewing mouthparts such as scale, moths, and aphids. In 2001, a total of 93,055 pounds of methidathion were applied in California. The highest uses were in stone fruits, citrus, artichokes, walnuts, almonds, and to a lesser extent olives. Methidathion may be applied aerially or by ground equipment. Although methidathion has a low vapor pressure and is relatively non-volatile, residues of this chemical may be found in ambient air during the summer growing season.

2. Methidathion is moderately water-soluble and has the potential to run off into surface water depending on use conditions and environmental factors. Methidathion has been detected in California surface water as a result of rain runoff from wintertime dormant spray applications. The reported aqueous photolysis half-life of methidathion is 8.2 days. Methidathion has a low likelihood of leaching to ground water due to its relatively short soil half-life (1.5 – 8 days); methidathion has not been detected in California ground water. Microbial degradation appears to be the dominant route for methidathion breakdown.

3. Ambient air monitoring data for methidathion is available from four sites located within 0.25 miles of citrus groves: Sunnyside Elementary School in Strathmore, Jefferson Elementary School in Lindsay, Exeter Union High School in Exeter and the University of California Lindcove Field Station in Exeter. Background samples were collected at the California Air Resources Board (ARB) Ambient Air monitoring Station in Visalia. The monitoring was conducted from June 27 through July 25, 1991. The Jefferson Elementary School site was the only location with samples above the limit of quantitation, so exposure estimates were based on the results obtained at this site. These monitoring data were used in the RCD/TAC document for estimation of acute, seasonal and chronic human exposure to methidathion in ambient air and also used by OEHHA in preparing these findings.

4. Air concentrations of methidathion during and after an application on an orange grove in Tulare County were also measured and the data used in the RCD/TAC document for estimating acute human exposure at application sites. Estimates for seasonal and chronic airborne exposures for the hypothetical individual residing adjacent to application site(s) were not provided in the RCD/TAC.

5. Exposure values presented in the RCD/TAC document were estimated as follows:

   a) Average daily doses (ADD) were calculated for acute exposures in ambient air based on the 95th percentile air concentration of methidathion measured at the Jefferson site;
   b) Seasonal average daily doses (SADD) were calculated for seasonal exposures from the average air concentration at the Jefferson site; and
   c) Annual average daily doses (AADD), based on a seven-month annual use period, were calculated for chronic exposures.

   Seasonal and chronic dose estimates were calculated from ambient air concentrations from the Jefferson Elementary School site only and not for individuals living adjacent to an application site. Human doses were estimated for adults and children (1-6 years) and were based on generally accepted default values for body weights and breathing rates. In preparing these findings, OEHHA recalculated exposure estimates assuming 100 percent inhalation absorption, rather than the 50 percent value used in the RCD/TAC document (see also Finding 23 and Tables 1 and 2). Additionally, OEHHA estimated seasonal and chronic exposures for application site air.

6. Human exposure to atmospheric methidathion can occur by both inhalation and dermal routes, but the predominant exposure route for systemic doses is inhalation. Inhalation uptake was assumed in the RCD/TAC document to be 50 percent for these estimates. Since no chemical-specific value for the inhalation absorption of methidathion has been established, OEHHA assumes 100 percent absorption of the material by the inhalation route. Dermal uptake of methidathion has not been quantitatively estimated in these studies but it is expected to provide less than 1 percent of the systemic dose received by inhalation.

Health Effects Studies

Humans

7. Numerous reports of acute pesticide illness involving methidathion have been reported in California over the past several years. Between 1982 and 2001, a total of 109 incidents were reported associated with the use of methidathion. Thirty of these incidents involved the use of methidathion as the sole active ingredient. Most of these cases (74 percent) were systemic in nature including complaints of vomiting, nausea, abdominal cramps, headache and dizziness. The putative route of exposure for the majority of these acute illnesses is inhalation. The remaining cases were incidents of localized dermal irritation. Most of the cases were exposures to agricultural workers either as a direct result of their

handling of the material or field workers experiencing drift from nearby applications. Only three incidents were non-occupational.

Animals

8. The acute toxicity of methidathion has been evaluated in a variety of animal species including rats, mice, guinea pigs, rabbits, hamsters and pigeons. Signs of acute intoxication with methidathion are cholinergic in nature and consist of dizziness, ataxia, irregular and increased respiration, dyspnea, fasciculations, trembling, salivation, exophthalmos and death. Oral LD_{50}s range from 25 to 80 mg/kg in rats. Dermal LD_{50}s range from a low of 85 mg/kg in rats to 155 mg/kg in rabbits. Technical grade methidathion was a moderate to severe dermal sensitizer in the guinea pig.

9. Six oral and six dermal subchronic toxicity studies in laboratory animals are available. Clinical signs following subchronic exposure to methidathion included lethargy, anorexia, labored/rapid breathing, hunched posture, ataxia, tremors, soft feces and low body temperature. Pathological findings revealed anemia, liver toxicity, reduced brain cholinesterase (ChE) activity, and lesions of the liver, stomach and heart following subchronic exposure to methidathion. From these studies, a subchronic NOAEL of 1 mg/kg/day for inhibition of brain ChE and lesions in the liver and gallbladder of rabbits at the next higher dose of 10 mg/kg/day (21-day dermal exposure) was identified (Osherhoff, 1987).

10. Six chronic toxicity/oncogenicity feeding studies are available for methidathion, two in rats, two in mice and two in dogs. One chronic gavage study is available in the rhesus monkey. Effects observed in chronic studies were similar to those observed following subchronic exposure; however, hepatotoxicity was more prevalent. The lowest NOAEL from an acceptable study was 0.15 mg/kg/day based on elevated liver enzymes in the serum and histological lesions observed in the livers of dogs at the next higher dose of 1.33 mg/kg/day (Chang and Walberg, 1991). An oncogenic response was observed in male mice and is discussed in Findings 11 and 18, below.

11. Methidathion genotoxicity data are mixed. However, positive results have been noted in a gene conversion/forward mutation assay with Saccharomyces cerevisiae (Arni and Muller, 1981), and in *in vitro* sister chromatid exchange (SCE) assays using Chinese hamster V79 cells (Chen *et al*., 1981) and human lymphocytes (Kevekordes *et al*., 1996).

12. A dose-related increase in liver tumors in male mice was observed in two long-term bioassays (IBT, 1980; Goldenthal, 1986). No evidence of oncogenicity was observed in female mice or either sex in the two rat bioassays. The incidences of hepatocellular adenoma and carcinoma, combined were 9/46, 15/45, 11/47, 21/43, and 38/45 for doses of 0, 0.4, 1.4, 6.7, or 13.1 mg/kg/day, respectively. The incidences combined were statistically different from the controls at $p < 0.01$ or less at the two highest doses. A cancer potency was derived from this dataset and is discussed in Finding 18.

13. Four reproductive toxicity studies are available in rats for methidathion (two single generation studies, one two generation study and one three generation study). Effects

observed in parental animals were tremors, alopecia, reductions in feed consumption and body weights, and reduced mating indices. Effects observed in pups included tremors, signs of maternal neglect, reduced pup weights, and reduced survival. A parental NOAEL of 0.4 mg/kg/day was identified based on alopecia, tremors, reduced mating index and poor maternal care (as evidenced by pups being cool to the touch, weak, starving and lethargic) observed at the next higher dose of 2.2 mg/kg/day (Salamon, 1987). A reproductive NOAEL of 0.4 mg/kg/day was identified from the same study as the parental NOAEL and was based on reduced pup weights and signs of maternal neglect observed at the next higher dose (2.2 mg/kg/day). No evidence of increased postnatal sensitivity was observed in these studies.

14. Several developmental toxicity studies in rats (3) and rabbits (2) are available for methidathion. Maternal effects observed included labored respiration, exophthalmia, miosis, chromodacryorrhea, vaginal bleeding, lethargy, stool alterations, loss of righting reflex, tremors, salivation, lacrimation, convulsions, ataxia, reduced food consumption and body weights, and death. Notable effects on the fetus were reduced ossification of the sternebrae and reduced body weights. A maternal NOAEL of 1.0 mg/kg/day was identified in rats based on mortality, clinical signs, and a reduction in feed consumption and body weights at the next higher dose of 2.5 mg/kg/day (Mainiero et al., 1987). A developmental NOAEL of 2.5 mg/kg/day based on reduced ossification of the sternebrae and reduced body weights at the next higher dose of 5.0 mg/kg/day was observed in a separate rat study (Fritz, 1976). This later study suffered from several deficiencies, the most significant of which (no food consumption data or analysis of test material) resulted in a low confidence in the dose estimation. Accordingly, it is relevant to point out that no developmental effects were observed in pups at the highest dose tested (2.5 mg/kg/day) in the Mainiero, 1987 study.

15. A number of neurotoxicity studies have been performed in hens and rats. No evidence of delayed neuropathy was observed in any of the five available hen studies. Three studies were conducted in rats, two were single-dose acute studies and one was a 90-day subchronic study. In the acute studies with rats, signs typically associated with inhibition of cholinesterase were observed: salivation, lacrimation, diarrhea, tremors, ataxia and muscle fasciculations. In all rat studies, signs of neurotoxicity were observed in the functional observational battery (FOB): changes in autonomic and CNS signs, sensorimotor effects, impaired neuromuscular functions, reduction in maze activity, and reduced body temperature. Significant inhibition of cholinesterase activity versus the controls was also observed in all rat studies in serum, red blood cells (RBC) and brain. An acute LOAEL of 1 mg/kg was identified based on cholinesterase inhibition in the cerebral cortex of male rats (59 percent of controls) at the time of peak effect (1.5 hours post-dosing); no NOAEL was observed in the study (Chang and Richter, 1994). A subchronic NOAEL of 0.2 mg/kg/day was identified in the 90-day rat study and was based on reduced ChE activity in the cerebral cortex and striatum (males – 74 percent of controls, weeks 2-3; females 63 percent of controls at week 13, respectively) at the next higher dose of 0.6 (males) or 0.7 mg/kg/day (females) (Chow and Turnier, 1995).

Basis, Potency, and Range of Health Risks to Humans

16. Human health risks for acute exposures to methidathion are estimated in the RCD/TAC document based on the estimated NOAEL of 0.3 mg/kg for inhibition of cholinesterase (59 percent of controls) in the cerebral cortex of male rats at the lowest dose tested, 1 mg/kg (Chang and Richter, 1994). The NOAEL was estimated in the RCD/TAC document from the LOAEL of 1 mg/kg by dividing the latter by an uncertainty factor (UF) of three. The endpoint was considered to be "mild" because: 1) no significant blood ChE inhibition was observed at the LOAEL; 2) only one region of the brain in one sex was affected; 3) the cortex was not uniquely sensitive to ChE inhibition at higher doses; 4) neurological signs were not observed in the FOB in either sex until 8 mg/kg; and 5) males were not more sensitive than females based on neurological signs. Thus, the RCD/TAC document used an UF of three.

17. OEHHA identifies the same study (Chang and Richter, 1994) for evaluating acute exposures to methidathion, however, we consider the inhibition of brain cholinesterase to be a significant adverse effect. We note that at dose levels of 8 and 16 mg/kg, statistically significant neurological signs were observed in males and that neurological signs were also reported for female rats at 1 and 4 mg/kg and that statistically significant inhibition of ChE activity in three regions of the brain and reductions in serum ChE activity were reported at 4, 8, and 16 mg/kg. Furthermore, we consider brain cholinesterases to be the most important targets for cholinesterase inhibitors and agree with the statement in the RCD/TAC: "…brain ChE inhibition to be indicative of overt toxicity since it is one of the primary functional target sites and more subtle central neurological signs, such as memory and learning losses, may not be easily detected in animals unless they are specifically tested for these effects." Accordingly, OEHHA applies an UF of 10 for the LOAEL to NOAEL conversion, and estimates an acute NOAEL of 0.1 mg/kg.

18. Human health risks from seasonal exposure to methidathion are estimated in the RCD/TAC document based on a subchronic NOAEL of 0.2 mg/kg/day identified in a 90-day rat study that was based on reduced ChE activity in the cerebral cortex and striatum (males – 74 percent of controls, weeks 2-3; females 63 percent of controls at week 13, respectively) at the next higher dose of 0.6 (males) or 0.7 mg/kg/day (females) (Chow and Turnier, 1995). Risks to human health from chronic exposure to methidathion are estimated in the RCD/TAC document based on the NOAEL from a chronic study of 0.15 mg/kg/day that was based on elevated liver enzymes in the serum and histological lesions observed in the livers of dogs at the next higher dose of 1.33 mg/kg/day (Chang and Walberg, 1991). OEHHA adopted the same subchronic and chronic NOAELs as in the RCD/TAC document for calculating MOEs and references exposure levels (RELs).

19. Oncogenic potency was quantified in the RCD/TAC because of the dose-related increases in hepatocellular adenomas and carcinomas in male mice observed in two separate bioassays and the limited positive genotoxicity data available in the literature. Cancer potencies of 0.34 (maximum likelihood estimate, MLE) and 0.53 $(mg/kg/day)^{-1}$ (95 percent upper confidence limit of the dose-response curve, 95% UCL) were calculated from the Goldenthal, 1986 bioassay using the multistage Weibull time-to-tumor model and assuming a linear dose-response. These methods were used in the document to

estimate cancer risks from lifetime exposures to methidathion. OEHHA adopted these cancer potencies for estimating oncogenic risks from airborne exposure to methidathion.

20. Margins of exposure (MOEs) were calculated in the RCD/TAC document for children and adults by dividing the NOAEL by the estimated exposure. Acute exposures were assessed for application site scenarios and acute, seasonal and chronic exposures were assessed for ambient air scenarios. MOEs exceeding 100, when based on NOAELs from animal studies, are generally considered by DPR to be sufficiently protective of human health.

21. MOEs presented in the RCD/TAC for acute exposures of residents adjacent to a methidathion application ranged from 1,300 to 2,600 for children and adults, respectively. Acute MOEs for ambient exposure were all greater than 100 and ranged from 2,100 to 4,300 for children and adults, respectively.

22. MOEs presented in the RCD/TAC for seasonal exposures to methidathion presented in the RCD/TAC document ranged from 8,000 to 17,000 for children and adults, respectively. MOEs for chronic exposures ranged from 10,000 to 21,000 for children and adults, respectively. Seasonal and chronic exposures were not estimated in the RCD/TAC for individuals living adjacent to an application site.

23. Oncogenic risk estimated in the RCD/TAC from exposure to methidathion in the ambient air ranged from 2.4×10^{-6} at the maximum likelihood estimate (MLE) to 3.7×10^{-6} at the 95 percent upper confidence limit on the slope of the dose-response curve (95 percent UCL). An estimated risk of 1×10^{-6} or less is typically considered negligible. Accordingly, OEHHA believes that lifetime exposure to methidathion in the ambient air presents a potential public health concern.

24. OEHHA estimates exposures and calculates MOEs and cancer risks differently than they are calculated in the RCD/TAC. OEHHA assumes 100 percent inhalation absorption of the chemical versus 50 percent as is assumed in the document (Finding 6). Next, for acute MOEs, OEHHA uses a NOAEL of 0.1 mg/kg versus the 0.3 mg/kg used in the RCD/TAC (Finding 16). Lastly, because individuals may live adjacent to an application site or several application sites, OEHHA has evaluated seasonal and chronic exposures to these hypothetical receptors (Findings 4, 24 and 25; Tables 1 and 2).

25. For acute exposures of residents living adjacent to application sites, OEHHA's calculations result in MOEs of 217 and 433 for children and adults, respectively. Seasonal MOEs for application site air are 423 and 862 for children and adults, respectively. Chronic MOEs for application site air are 545 and 1111 for children and adults, respectively. MOEs calculated by OEHHA for ambient air exposures are, for children and adults, respectively; acute: 350 and 714; seasonal: 4,000 and 8,500; chronic: 5,000 and 10,500. Even though MOEs calculated by OEHHA are lower than those calculated in the RCD/TAC, all MOE values are greater than 100 suggesting that estimated exposures to methidathion are below levels considered to be of potential public health concern for non-cancer effects. A comparison of MOEs calculated in the RCD/TAC and by OEHHA can be seen in Table 1.

26. Oncogenic risk estimated by OEHHA would be twice that estimated in the RCD/TAC because 100 percent inhalation absorption was assumed versus the 50 percent value used in the RCD/TAC (Finding 6). Risks estimated by OEHHA for exposure to methidathion in the ambient air range from 4.8×10^{-6} at the MLE to 7.4×10^{-6} at the 95 percent UCL. Risks associated with application site air are estimated to be 4.6×10^{-5} at the MLE to 7.3×10^{-5} at the 95 percent UCL. As stated above, an estimated risk of 1×10^{-6} or less is typically considered negligible. Accordingly, OEHHA believes that lifetime exposure to methidathion in the ambient air presents a potential public health concern. A comparison of MOEs calculated in the RCD/TAC and by OEHHA can be seen in Table 2.

Table 1. Comparison of the MOEs[1] Calculated by DPR and OEHHA for Application Site and Ambient Air Exposures

Exposure Scenario	DPR MOE[2]		OEHHA MOE[3]	
	Child	Adult	Child	Adult
Application Site				
acute[4]	1,300	2,600	217	433
seasonal	n/a[5]	n/a	423	862
chronic	n/a	n/a	545	1,111
Ambient Air				
acute	2,100	4,300	350	714
seasonal	8,000	17,000	4,000	8,500
chronic	10,000	21,000	5,000	10,500

1. MOEs are calculated as follows: NOAEL/estimated exposure.
2. DPR assumed 50 percent inhalation absorption.
3. OEHHA assumed 100 percent inhalation absorption.
4. DPR applied a LOAEL to NOAEL conversion factor of 3 to estimate a NOAEL from the LOAEL of 1.0 mg/kg identified in the study of Chang and Richter, 1994. OEHHA applied a conversion factor of 10 to estimate a NOAEL.
5. Not applicable. MOEs for seasonal and chronic exposures for the application site scenario were not calculated in the RCD/TAC.

27. OEHHA calculated a single reference exposure level (REL) for each exposure duration: acute, seasonal, and chronic by dividing the oral NOAEL (mg/kg/day) by the breathing rate (m^3/kg/day) and uncertainty factor (unitless). All NOAELs were derived from

experimental studies in animals. Children's breathing rates were used for the calculations since children have higher breathing rate(s) per unit of body weight than do adults; hence, they experience the greatest exposure on a per-weight basis. Acute and seasonal RELs were calculated using the upper 95th percentile breathing rate for children of 0.581 m^3/kg-day. The chronic REL was based on a child's mean breathing rate of 0.452 m^3/kg-day. The distribution of children's breathing rates is described in OEHHA's Technical Support Document for Exposure Assessment and Stochastic Analysis (September, 2000). Uncertainty factors of 100 were applied to the NOAELs in consideration of the variability between and within species (100). This results in RELs of 1.7, 3.4 and 3.3 μg /m^3 for acute, subchronic (seasonal) and chronic exposures, respectively. RELs calculated by OEHHA are shown in Table 3.

Table 2. Comparison of Estimated Oncogenic Risk[1] for Lifetime Exposure as Calculated by DPR and OEHHA for Application Site and Ambient Air

Exposure Scenario	DPR MOE[2]		OEHHA MOE[3]	
	Maximum Likelihood Estimate	95 percent Upper Bound	Maximum Likelihood Estimate	95 percent Upper Conf. Level
Application Site	n/a	n/a	4.6×10^{-5}	7.3×10^{-5}
Ambient Air	2.4×10^{-6}	3.7×10^{-6}	4.8×10^{-6}	7.4×10^{-6}

1. Oncogenic Risk = oncogenic potency x exposure estimate. Potencies were calculated in the RCD/TAC and were: 0.34 $(mg/kg/day)^{-1}$ maximum likelihood estimate; 0.53 $(mg/kg/day)^{-1}$ 95 percent upper confidence limit estimate. Exposure estimates were the average annual daily doses as described in the RCD/TAC.
2. DPR assumed 50 percent inhalation absorption.
3. OEHHA assumed 100 percent inhalation absorption.
4. Not applicable. Oncogenic risks for application site scenarios were not calculated in the RCD/TAC.

Table 3. Reference Exposure Levels Calculated by OEHHA[1] for Acute, Seasonal and Chronic Exposures to Methidathion

Exposure Duration	OEHHA REL ($\mu g/m^3$)
Acute	1.7[2]
Seasonal	3.4[3]
Chronic	3.3[4]

1. Acute and seasonal RELs were calculated using the upper 95th percentile breathing rate for children of 0.581 m^3/kg-day. The chronic REL was based on a child's mean breathing rate of 0.452 m^3/kg-day. An uncertainty factor of 100 was applied to all calculations.
2. Chang and Richter, 1994, estimated NOAEL of 0.1 mg/kg based on a LOAEL of 1.0 mg/kg for inhibition of ChE in the rat cerebral cortex.
3. Chow and Turnier, 1995, NOAEL of 0.2 mg/kg/day based on inhibition of ChE in the rat cerebral cortex.
4. Johnston, 1967 ; NOAEL of 0.15 mg/kg-day for elevated liver enzymes in serum and hepatic lesions.

Other Relevant Findings

28. No sensitive subpopulations have been identified, including infants and children. U.S. EPA's Food Quality Protection Safety Factor Committee has recommended that the ten-fold safety factor not be used in methidathion risk assessments because of the presence of adequate data, and because there was no evidence of enhanced susceptibility of infants or children to the toxic effects of methidathion.

29. Limited information is available regarding the environmental breakdown products of methidathion. The extent of or any toxicological significance of co-exposure to possible breakdown products cannot be evaluated.

30. Cumulative exposure to other chemicals with similar mechanisms of action is likely. The extent of or any toxicological significance of cumulative exposure with these compounds has not been but should be evaluated.

31. The existing pesticide illness surveillance system is unable to characterize latent or chronic illnesses resulting from pesticide exposures. No epidemiological longitudinal cohort or follow-up studies exist in California that would delineate chronic illnesses arising from methidathion exposure.

32. Technical grade methidathion was a moderate to severe dermal sensitizer in the guinea pig. Sensitization is a potentially serious toxic effect. Use of this endpoint in risk assessment is problematic and sensitization risks are not assessed in the RCD/TAC.